Clinical Pharmacology and Use of Chlorothiazide in the Treatment of Hypertension

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When chlorothiazide is administered to a nonedematous hypertensive or normotensive individual there is within the first 48 to 72 hours of treatment a diuresis of sodium and chloride with a loss of approximately 250 to 300 mEq. of these ions over and above the level of intake. The serum concentrations of sodium and chloride do not change significantly. Accompanying the saluresis there is a loss of 1.5 to 2.5 kg. of body weight and a reduction of extracellular fluid space of approximately 1 to 2 liters. Thus, the salt and body weight losses can be accounted for almost entirely by the reduction in extracellular fluid space.[1]

Accompanying the loss of extracellular fluid space there is, of course, a reduction in plasma volume since these two spaces are in equilibrium. The reduction in plasma volume averages about 400 ml., a 15 to 20 per cent reduction, as has been shown by Dr. Dustan's group at the Cleveland Clinic

and by ourselves. All of these changes are well developed at the end of 48 hours of therapy. It is during this period also that the blood pressure falls in hypertensive patients. The extent of the hypotension is not great, averaging 15 per cent of mean blood pressure. In normotensive individuals, despite similar fluid compartment changes, there is no reduction of basal blood pressure, although there is an alteration in vascular reactivity which will be described later.

Crosley and his associates[2] have shown, and we have confirmed, that the hypotensive response to chlorothiazide is associated with a decrease in right heart pressures and cardiac output. Using the Hamilton method, Dustan also has found a reduction in cardiac output. It seems probable that the depletion of plasma volume and reduction of tissue pressure secondary to the interstitial fluid loss result in a fall of right heart filling pressures. It is not easy to explain why these factors do not call forth compensatory reflex vasoconstriction. Perhaps this failure is due to several factors: The reduction in total blood volume is neither very great nor very rapid, there is no loss of red cells, and hemodilution cannot take place because of the concomitant depletion of the interstitial fluid space.

If it is true that the reduction of arterial pressure is associated with a decline of cardiac output, which in turn is dependent on the reduction of plasma volume, then restoration of plasma volume should restore the arterial pressure. When hypertensive patients are infused with 500 ml. of 6 per cent dextran over a 15-minute period the blood pressure rises to, or very close to, the pre-chlorothiazide level.[3] The results are the same whether the dextran is dissolved in isotonic saline or in 5 per cent glucose in water. Thus, restoration of plasma volume rather than salt is essential for restoration of blood pressure.

Addition of salt is effective in restoring the blood pressure only if enough is given to elevate the plasma and extracellular fluid volumes. Since chlorothiazide is a highly potent saluretic agent, about 25 gm. of salt per day usually must be administered to produce the blood pressure reversal. Only when the amount of salt is elevated to a point sufficient to produce a gain in body weight will the blood pressure rise also.

These effects on plasma and extracellular fluid volumes are not temporary but continue as long as the drug is administered. Measurements taken at 8 to 12 months following initiation of treatment show maintenance of some reduction in these extracellular spaces. Discontinuation of chlorothiazide after these long periods of therapy results in a prompt restoration of extracellular volumes and of the blood pressure within 48 to 72 hours after the drug has been discontinued, provided that adequate amounts of salt are permitted in the diet.

The changes described are not unique for chlorothiazide. Similar effects on blood pressure, cardiac output and fluid volume compartments have been observed following parenteral mercurials. In patients taking the rice diet for several weeks, plasma volume depletion occurs and blood pressure can be restored either by supplying salt in the diet or by replenishing the plasma volume with salt-free dextran.[4] These various observations supply a unified, coherent and rational paradigm in a formerly confused field. The reason for the confusion in the literature[5, 6] probably lies in the difficulties attendant on obtaining accurate volume space measurements. Meticulous technique is required, and even then frequent rechecks are essential in order to detect discrepancies. For example, we used two different indicators, SCN and

radiosulfate or radiosodium, together in tracing the extracellular volume changes and repeated the determinations when these were discrepant. In regard to plasma volume, the hematocrit change served as an additional check on the method.

Although normotensive subjects respond to chlorothiazide with a similar saluresis and reduction of extracellular fluid compartments, they exhibit no change in basal blood pressure. However, as Merrill[7] and ourselves[8] have shown, the hypertensive response to norepinephrine infusion usually is reduced. Contrariwise, we have demonstrated that the hypotensive response to a depressor agent such as trimethaphan (Arfonad) is increased.[8] Therefore, although basal pressure is unaffected in normotensive subjects, chlorothiazide alters their vascular responsiveness. Their blood pressures become less reactive to pressor stimuli and more responsive to depressor agents.

The basal blood pressure of the hypertensive is affected by chlorothiazide probably because some abnormal pressure mechanism is operative in these patients. Chlorothiazide simply reduces their vascular reactivity to this unknown pressor mechanism. Blood pressure was affected even in the mildest forms of hypertension with basal diastolics of 90 mm.Hg and above. These results speak against Pickering's concept that moderate degrees of elevated blood pressure do not reflect an abnormal disease process but represent rather the individuals at the higher ranges of the distribution curve of normal blood pressures.[9] Our results with chlorothiazide indicate that at about 90 mm.Hg basal diastolic pressure a clear-cut separation exists between normal individuals and hypertensive patients.

If the normotensive, chlorothiazide-treated subject is given 500 ml. of salt-free dextran in order to replenish his plasma volume, the basal blood pressure does not change but the vascular responsiveness to pressor and depressor agents reverts immediately to the pretreatment level. Therefore, vascular reactivity is dependent in large measure on plasma volume.

In previous studies on norepinephrine and ganglion blocking drugs,[10] we pointed out the intimate relationship between total blood volume and the capacity of the vascular tree. In that connection we emphasized the importance of the sympathetic nervous system in altering postarteriolar as well as arteriolar tone. Sympathetic stimulation decreases peripheral vascular capacity and since blood volume remains unchanged, central venous and right heart pressures rise, with a resulting increase in cardiac output. Sympathetic inhibition produces exactly opposite results, with an increase in vascular capacity (in relation to effective blood volume) and a reduction in cardiac output.

It would appear that salt depletion also affects the relationship between blood volume and vascular capacity, in this case, however, by reducing effective blood volume rather than by increasing vascular capacity. The same reductions are produced, nevertheless, in central venous pressure and cardiac output. This, of course, explains why the combination of cholorothiazide and ganglion blocking agents has such great hypotensive potency. These considerations do not rule out the possibility that arteriolar reactivity is unaffected by the reduced plasma volume. Smooth muscle exhibits greater contractibility when it is stretched than when it is relaxed.

These studies also de-emphasize the importance of salt as an etiologic factor in hypertension. It is true that salt deprivation or salt depletion reduces the blood pressure of hypertensive patients. However, this seems to be due primarily to the resulting fall in plasma volume. Thus, the role of salt in

hypertension appears to be permissive rather than causative. If salt is available, a "normal" expansion of extracellular and plasma volume is permitted, thus allowing the unknown pressor mechanism in hypertension to function effectively.

Chlorothiazide has been remarkable for the lack of uncomfortable side reactions and apparent freedom from toxic effects. The reduction in extracellular fluid volume is in some way controlled at the desired level and does not proceed to the point of severe dehydration. Yet, a note of caution must be sounded. Depressions of serum potassium levels have been noted by all observers in patients treated for long periods of time.

Dr. Wilson in our laboratory has studied some of the patients who have been under chlorothiazide treatment for periods of 8 to 12 months without potassium supplements. In those with serum potassium levels below 3.5 mEq. she found also reductions in total exchangeable potassium and elevations of total exchangeable sodium. The latter occurred even though the extracellular fluid space remained reduced while the serum sodium concentration was essentially unchanged. Therefore, the excess exchangeable sodium must have been in the cells, where it was replacing the cellular depletion of potassium. This pattern is similar to that seen in chronic diarrheal states and may be a reflection of secondary aldosteronism stimulated by the reduction in cardiac output.

Regardless of cause, the reduction of total exchangeable potassium might have serious consequences over a long period of time. Potassium supplementation in an amount of 75 to 100 mEq. per day seems indicated in all patients who exihibit an abnormally low level of serum potassium. It is hoped that this will be sufficient to maintain the patient in reasonably normal electrolyte balance. Perhaps in the future aldosterone antagonists will be developed which will combat the depletion of body potassium.

One could surmise from the alteration in vascular reactivity produced by chlorothiazide that the drug would be most effective in enhancing the antihypertensive action of other blood pressure reducing drugs. Indeed, this was the first observation made with this agent in hypertensive patients.[11] Of the various antihypertensive compounds that can be used with chlorothiazide, our experience indicates that hydralazine in doses not exceeding 150 mg. per day is in general the most effective and best tolerated regimen for moderate hypertension. In severe cases ganglion blocking agents with reserpine and chlorothiazide provide a potent and reasonably well tolerated combination. Allowance, however, always must be made for problems posed by individual cases, and the above regimens are suggested only as useful starting points in the therapeutic experiment posed by each patient.

REFERENCES

1. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Chlorothiazide in hypertensive and normotensive patients. Ann. New York Acad. Sc., *71*:450, 1958.
2. Crosley, A. P., Jr., Castillo, C., Freeman, D. J., White, D. H., Jr., and Rowe, G. G.: The acute effects of carbonic anhydrase inhibitors on systemic hemodynamics. J. Clin. Invest., *37*:887, 1958.
3. Wilson, I. M., and Freis, E. D.: Extracellular fluid and plasma volume changes in nonedematous hypertensives after prolonged treatment with chlorothiazide. Circulation, *18*:800, 1958.
4. O'Donnell, T. V.: In Smirk, F. H.: High Arterial Pressure. Charles C Thomas, Springfield, Ill., 1957, p. 432.

5. Hollander, W., and Chobanian, A. V.: The mode of action of chlorothiazide and mercurial diuretics as antihypertensive agents. J. Clin. Invest., *37*:902, 1958.
6. Winer, B. M.: Studies of the content and distribution of sodium, potassium and water in arterial hypertension. Circulation, *18*:800, 1958.
7. Merrill, J. P., Guinand-Baldo, A., and Giordano, C.: The effect of chlorothiazide on norepinephrine response in human hypertension. Clin. Res., *6*:230, 1958.
8. Wanko, A., and Freis, E. D.: Altered vascular responsiveness following chlorothiazide or mercurial diuresis in normotensive subjects. Circulation, *18*:792, 1958.
9. Pickering, G. W.: The concept of essential hypertension. Ann. Int. Med., *43*:1153, 1955.
10. Freis, E. D., and Rose, J. C.: The sympathetic nervous system, the vascular volume and the venous return in relation to cardiovascular integration. Am. J. Med., *22*:175, 1957.
11. Freis, E. D., and Wilson, I. M.: Potentiating effect of chlorothiazide (Diuril) in combination with antihypertensive agents. Med. Ann. D. C., *26*:468, 1957.